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09/725,010	11/29/2000	Paula Sundstrom	23878.0005	8550

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/725,010	SUNDSTROM, PAULA	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7-7-04.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,21 and 28-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,21 and 28-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 7-7-04.

Claims 1, 21, 28-32 are pending in the instant application.

The declaration under 37 CFR 1.132 filed 7-7-04 is insufficient to overcome the rejection of claims 1, 21, 28-32 based upon 112, first paragraph as set forth in the last Office action for the reasons elaborated below.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 21, 28-32 are rejected under 35 U.S.C. 112, first paragraph, for lacking adequate written description for the reasons of record set forth in the Office actions mailed 7-2-03 and 4-7-04, and elaborated below.

Applicant's arguments filed 7-7-04 have been fully considered but they are not persuasive. Applicants argue that the experiments described in the instant disclosure and the declaration filed by Dr. Sundstrom on 7-7-04 provide adequate written description for the claimed invention.

The claims are drawn to a method of inhibiting attachment of *C. albicans* to human tissue by interfering with DNA binding proteins specific to UAS regions of the HWP1 promoter present during germ tube formation in *C. albicans*.

Applicants argue that portions of the specification (e.g. pp. 1-2, 6, 8, 10-11, 21-22, 24, 26, 53, 55, 62, 64-68, 72 and 75 and figures 1-5) fully and adequately describe the claimed invention.

Pages 1-2 of the specification provide a general discussion of fungi and *C. albicans*. Page 6 describes the 5' flanking regions of HWP1 to be SEQ ID NO: 1, as well as describing the purported NIT-2 binding domains, and lists DNA BP candidates for these purported regions to include GAT 99, GAT1 and GATA-like BP. Pages 7-8 describe the figures, including figures 1-5: Figure 1 describes the disruption of HWP1 with URA3; figure 2 compares the survival of gnotobiotic nude mice orally colonized with either HWP1 (where mice are less able to thrive) or with the null mutant of HWP1 (more able to thrive upon oral colonization with *C. albicans*); figure 3 is a depiction of the 5' flanking region of HWP1; figure 4 characterizes the 5' flanking sequences of HWP1 in terms of purported DNA BP binding sites, including purported TATA box, NIT-2 binding sites, MATA, PO4 and HSF sites; figure 5 provides a comparison between previously identified GAT99 and the purported NIT-2 binding domain of HWP1. Pages 10-11 of the specification describe a correlation between reporter (GFP) expression and germ tube formation, whereby GFP is operably linked and downstream of the 5' flanking sequences of HWP1. The generation of nested deletions of the 5' flanking sequence of HWP1 using PCR is also described here. Pages 21-22 review a precedent in the art for

a correlation between pro-invasive factors and hyphal growth. Page 24 reviews signal transduction pathways existing in S cerevisae. Page 26 describes methods that can be used to identify UAS and URS in the 5' region of HWP1. Pages 53-54 describe the ability of germ tubes to attach to BECs when HWP1 is functionally expressed, and the lack of attachment by null mutants of HWP1. Pages 54-55 illustrate purported DNA BP binding sites of the 5' flanking regions of HWP1 based on sequence comparison with previously identified DNA BP binding sites. Page 62 describes deletion mutants generated in the 5' flanking regions of HWP1 and electrophoretic mobility shift assays (EMSA) performed using HWP1 5' flanking DNA and crude hyphal protein extracts. Pages 67-68 are proposed experiments to identify the purported hyphal DNA BP, using either reverse cloning of cDNA library screening techniques. Page 72 also has proposed experiments to determine relationships between hyphal specific genes and the presence of putative DNA BPs. These correlation between these teachings and the written description and enablement requirements are addressed below.

Applicants argue that the GFP reporter experiments assess the role of the nucleotide sequences upstream of the coding region on HWP1 of SEQ ID NO: 1, which sequences mediate expression of HWP1 in response to hypha inducing conditions. Applicants are correct that a correlation exists between HWP1 expression and hypha inducing conditions. But, contrary to Applicants' assertions, this correlation does not provide adequate description of the genus comprising DNA BP specific to UAS regions of the promoter of HWP1. It does suggest that either activators of (or antagonists of inhibitors) of HWP1 are expressed during hypha inducing conditions. Contrary to

Applicants' assertions, this correlation is not representative of an adequate description of the genus comprising DNA BPs that specifically bind to UAS of HWP1, but instead suggests their presence.

Applicants argue that HWP1 is not expressed upon deletion of its 5' flanking sequences of HWP1. Applicants are correct that HWP1 expression appears to be dependent upon the presence of these 5' flanking sequences of HWP1. This provides evidence that the regulation of HWP1 expression resides in these sequences, but, contrary to Applicants' assertions, it does not provide an adequate description of what the activators (or de-repressors) are that act on this portion of the HWP1 gene.

Applicants argue that the gel retardation assays showing gel retardation of the 5' flanking sequences when mixed with germ tube derived crude extracts, combined with the requirement of the presence of the 5' flanking sequences for HWP1 expression, together provide adequate support and describe the instantly claimed invention. Contrary to Applicants assertions, the gel retardation assays in the presence of crude (protein) extract from germ tubes suggest that DNA BP binding is occurring on the 5' flanking region of the HWP1 gene, but this does not provide any characterization of the purported DNA BP's, it instead strongly suggests their existence. Adequate written description requires a description of the concise structural features of the genus claimed, not the possibility or probability of the existence of its members.

Applicants argue that the correlation between 90% expression and the presence of 1902 bp upstream sequences indicate that the sequences most responsible for promoter activation were found within this region. Contrary to Applicants' assertions,

the requirement for these sequences for HWP1 expression does not replace the requirement for a concise description of the purported binding proteins that are instantly claimed in order for the genus to be adequately described.

Applicants argue that the additional deletion experiments (e.g. –1063, -555, -803) allow for one to conclude that basal activation activity resides in some portions of the region, while more robust activation is attributed to a more distal region of the 5' UTR, while a repressing region exists between nt –1410 and –1366. Applicants are correct that activating and repressing functions have been located in the various regions of the 5' flanking region of HWP1. Contrary to Applicants' assertions, however, these correlated activating and repressing functions are not representative of the concise structural features required for the adequate written description of the purported DNA BP(s) claimed.

Applicants additionally argue that the EMSA experiments using the identified cis activating regions of the 5' flanking sequences of HWP1 show the presence of DNA binding proteins that bind to the UAS regions of the HWP1 promoter. Applicants are correct that the presence of DNA binding proteins is supported by these gel retardation results. But, contrary to Applicants' assertions, the presence of such purported binding entities that provide a decreased electrophoretic mobility of the 5' flanking DNA fragments of HWP1 indicate the presence of binding entities, but do not provide an adequate description of these entities' molecular properties or amino acid sequences. Therefore, the observation of decreased electrophoretic mobility, in the absence of further characterization/description of the molecular properties or the core structural

features of the genus claimed, is not representative of an adequate description of the claimed genus' concise structural features.

Applicants argue that the correlation of 5' fragment binding by retardation assays with germ tube extracts only (and not yeast extracts), and which binding is competed by specific DNA but not by non-specific DNA, fully describes the claimed invention. Contrary to Applicants' assertions, the localization of fragments that show purported DNA BP binding using gel retardation assays, the specificity of the DNA that binds, and the correlation with germ tube and not yeast as a source of BPs, do not provide sufficient representation of the concise characteristics of the genus claimed, comprising DNA BPs specific to UAS of HWP1.

The specification and declaration describe the various regions of the HWP1 promoter that are purported binding regions for the purported DNA binding proteins involved in modulating promoter activity (e.g. figures 1, 4, 5 and 14; pages 12, 25, 26, 54 and 56 of the instant specification). The specification and declaration also describe the relationship between modulation of promoter activity and germ tube formation in hyphae, and the lack of promoter modulation in yeasts (e.g. figures 11 and 13; pages 60-62 of the instant specification; pages 2 and 5 of the declaration). But contrary to Applicants' assertions, the detection of purported DNA protein binding to HWP1 promoter regions using gel retardation assays, however, does not provide adequate written description of the common structural features, or of a representative number of species of the genus comprising DNA binding proteins specific to UAS regions of the HWP1 promoter, nor for their inhibition in binding to UAS regions of the HWP1

promoter, nor for the ability to inhibit the attachment of *C albicans* to human tissue in an organism. Therefore, the rejection for lack of written description for the genus comprising DNA binding proteins specific to UAS regions of the HWP1 promoter is maintained.

Claims 1, 21, 28-32 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed, for the reasons of record set forth in the Office actions mailed 7-2-03 and 4-7-04, and elaborated below.

Applicant's arguments filed 7-7-04 have been fully considered but they are not persuasive. Applicants argue that the specification and declaration by Dr. Sundstrom, filed 7-7-04 demonstrate that the instant invention is fully enabled over the scope claimed.

The claims are drawn to a method of inhibiting attachment of *C. albicans* to human tissue by interfering with DNA binding proteins specific to UAS regions of the HWP1 promoter present during germ tube formation in *C. albicans*.

The specification and declaration teach correlating expression patterns of HWP1 mRNA with development of *C. albicans*; for detecting an increase in HWP1 mRNA in *C. albicans* when grown under inducing, compared to repressive, conditions; for the characterization of HWP1 promoter sequences that are modulated in response to hypha inducing conditions; for an in vitro method of characterizing hyphal specific *C. albicans* DNA BP binding to the HWP1 promoter (of SEQ ID NO: 1); and for correlating a failure of mice to thrive with orally colonized *C. albicans*, compared to mice infected with a null mutant strain (HWP$^-$ *C. albicans*). Contrary to Applicants' assertions, however, the

specification and declaration are not enabling for, nor representative of the ability to inhibit attachment of *C albicans* to human or other animal tissue by interfering with DNA binding proteins specific to UAS regions of the HWP1 promoter present during germ tube formation. The claims read broadly on the ability to inhibit *C albicans'* attachment to human tissue following inhibition of DNA binding protein (DNA BP) binding specifically to UAS regions of *C. albicans* to HWP1 in vivo and in vitro.

No evidence has been provided for the ability to inhibit attachment of *C albicans* to human tissue following administration of any inhibitors of DNA BP specific for the UAS regions of the HWP1 promoter. The ability of null mutant strains of HWP1 to survive orally colonized *C albicans* is not representative of the ability to inhibit DNA BP binding specifically to UAS regions of the HWP1 promoter in vitro or in vivo following administration of any DNA BP inhibitors. In view of the lack of guidance in the specification and the unpredictability associated with the targeting, efficient cellular uptake or inhibition of DNA BP binding specific to UAS regions of HWP1 in *C. albicans* in vitro or in vivo, and further whereby *C albicans* attachment to human tissue is inhibited in that organism, one of skill in the art would reasonably conclude that the instant disclosure is not enabling for the scope claimed. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of existing inhibitors, modes of their delivery and formulations to target *C. albicans* in an organism whereby DNA BP binding specifically to the UAS regions of the HWP1 promoter is inhibited in sufficient quantity in vivo, and attachment to human tissue is inhibited. Since the specification fails to provide any particular guidance for the

administration of any inhibitors of DNA BP binding specifically to UAS regions of HWP1 of *C. albicans* in an organism or in vitro, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 31, line 1, "said NIT2 DNA binding domain" lacks proper antecedent basis. Replacing "said" with –the—would be remedial.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
9-12-04

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